

AN INTERNATIONAL CLASSIFICATION OF RETINOPATHY OF PREMATURITY: CLINICAL EXPERIENCE*

BY *John T. Flynn*, MD

INTRODUCTION

"HAVE WE A SATISFACTORY CLASSIFICATION FOR RETINOPATHY OF PREMATURITY† (ROP)?" To get an answer to this, we must begin with history. In 1952, at the end of the decade of confusion and ambiguity over the nature of the disease process and its clinical course, Reese and co-workers¹ brought some degree of order by classifying the disease in a way that was immediately accepted by the ophthalmic and pediatric community. It quite succinctly described the observations all were making at that time with the monocular direct ophthalmoscope, the only instrument then available for observation of the fundus of the eye. As data from the studies on the role of oxygen²⁻⁴ began to emerge, leading to its curtailment and subsidence of the disease in its epidemic aspects, interest in further classification seemed illogical and impractical. The Reese classification¹ nicely encompassed all needs for a clinical description of the disease.

When ROP emerged again in the early 60s and 70s, ophthalmologists were in possession of better tools to observe and describe what they saw. Among these tools were the binocular indirect ophthalmoscope and fluorescein angiography.⁵ As a result, a series of observations by a number of authors⁶⁻¹¹ resulted in a clearer picture of the disease as it occurs in

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†The term "retinopathy of prematurity" is preferred in this paper because it can be utilized to describe all phases of the acute retinal changes observed in premature infants. The traditional term, "retrolental fibroplasia," is inappropriate in the acute phase of this disorder.

today's smaller and more fragile premature infant. Several further classifications of ROP based on these observations emerged. These new classifications¹²⁻²⁰ have each refined our understanding of the acute disease but failed in one respect or another to furnish the clinician with a complete picture of ROP as it is observed today. However, they did not stray far from the ground broken earlier by Reese and associates.¹ It therefore became apparent over time that all current classifications failed to unify today's observation in a useful manner as had Reese's earlier system. Furthermore, the real incidence of the disease may be increasing although the evidence on this point is inconclusive. Finally, treatment of the disease in its active and cicatricial forms has been advocated but it is not always clear what disease stage is being treated and what the results of such treatment are. Hence, the need for a new classification system.

CLASSIFICATION

The first and most important weakness of all current classification systems is that they fail to specify two critically important observable characteristics of the disease: its *location* in the retina and the *extent* of the developing retinal vasculature involved.

A group of 23 ophthalmologists representing 11 countries, sharing a common interest in ROP, met three times over a period of 2 years to develop a new classification system. The product of their deliberations, "An International Classification of Retinopathy of Prematurity,"²¹ has been submitted for publication to ophthalmic and pediatric journals in several countries. The advance that this classification system represents is that it embodies in its core the location and extent of the disease as well as its accurate staging.

LOCATION

For specification of this variable, the retina is divided into three zones (Fig 1). Each zone is concentric and centered on the optic disc rather than the macula, contrary to standard retinal drawings. This new scheme was selected because normal retinal vascular growth proceeds outward from the optic disc to the ora serrata in an orderly fashion.

Zone I consists of a circle, the radius of which subtends an angle of 30° and extends from the disc to twice the distance from the disc to the center of the macula. The limits of the zone are consequently defined in all directions as twice the disc-fovea distance.

Zone II extends from the edge of zone I peripherally to the nasal ora serrata. It extends around temporally to an area near the anatomic equator.

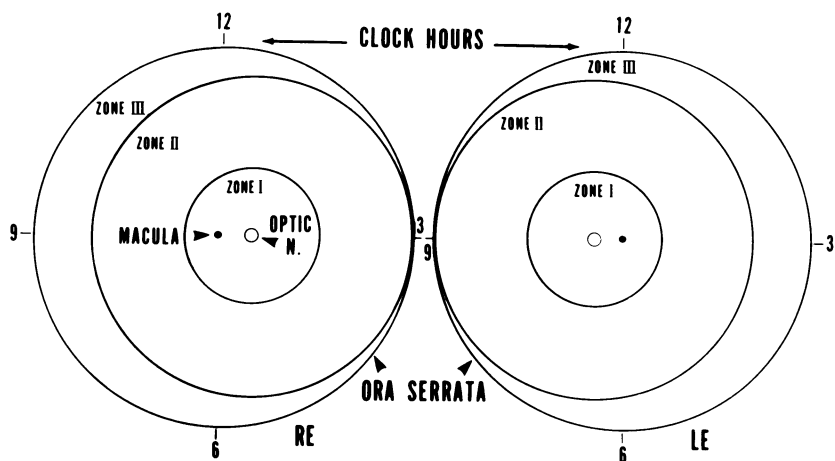


FIGURE 1

Schematic illustration of retina of right and left eye showing zone borders and the clock hours employed to describe location and extent of ROP.

Zone III is the residual crescent of retina anterior to zone II. This is the zone that is last vascularized in the premature eye and it is the zone, by common agreement of clinicians, most frequently involved with ROP.

EXTENT OF THE DISEASE

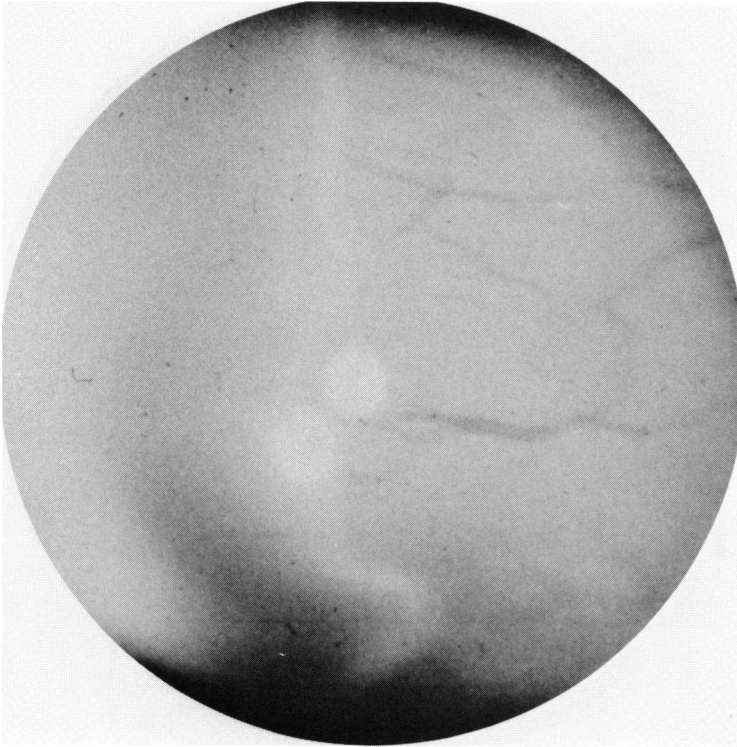
This is specified as hours of the clock. As the observer looks at each eye, 3 o'clock is to the right and nasal in the right eye and temporal in the left eye. Nine o'clock is to the left and temporal in the right eye and nasal in the left eye.

STAGING OF THE DISEASE

In addition to the above two parameters, the final one to be specified is the level of abnormal vascular response observed. Here, four stages which merge gradually into one another are recognized and staging for the eye as a whole is by the most severe manifestation present.

Stage 1. Demarcation line (Fig 2). This line is a thin but definite structure that separates the avascular retina anteriorly from the vascularized retina posteriorly. Vessels branch into abnormal arcades leading up to the line. It is relatively flat, white in color, and lies in the plane of the retina.

Stage 2. Ridge (Fig 3). The line of stage 1 now has grown, has height and width, occupies a volume, and extends up out of the plane of the

**FIGURE 2**

Fundus photograph illustrating demarcation lines of stage 1.

retina. The ridge may change in color from white to pink and the vessels may leave the plane of the retina to enter it. Small isolated tufts of new vessels lying on the surface of the retina may be seen posterior to this ridge structure but such lesions do not constitute the fibrovascular growth necessary for stage 3.

Stage 3. Ridge with extraretinal fibrovascular proliferation (Fig 4). To the ridge of stage 2 is added the presence of extraretinal fibrovascular proliferative tissue. The characteristic locations where this proliferating tissue may be found are: (1) continuous with the posterior aspect of the ridge, causing a ragged appearance of the ridge, (2) immediately posterior to the ridge but not always appearing connected to it, and (3) into the vitreous perpendicular to the retinal plane.

Stage 4. Retinal detachment (Fig 5). To the above is added unequivocal detachment of the retina. It may be caused by an exudative effusion of



FIGURE 3

Fundus photograph illustrating development of ridge characteristic of stage 2.

fluid, traction, or both, even in this early stage. It may be difficult to define, particularly when the detachment is shallow and posterior.

"PLUS" DISEASE

Progressive vascular incompetence, occurring along with the changes described at the edge of the abnormally developing retinal vasculature, is noted by increasing dilatation and tortuosity of the peripheral retinal vessels, iris vascular engorgement (Fig 6), pupillary rigidity, and vitreous haze. When, and only when, the vascular changes are so marked that the posterior veins are enlarged and the arterioles are tortuous, then the designation "plus" is added to the ROP stage (Fig 7).

RECORDING THE RESULTS

For purposes of recording the results of the examination, an examination record has been devised (Table I). The scheme is computer-compatible.

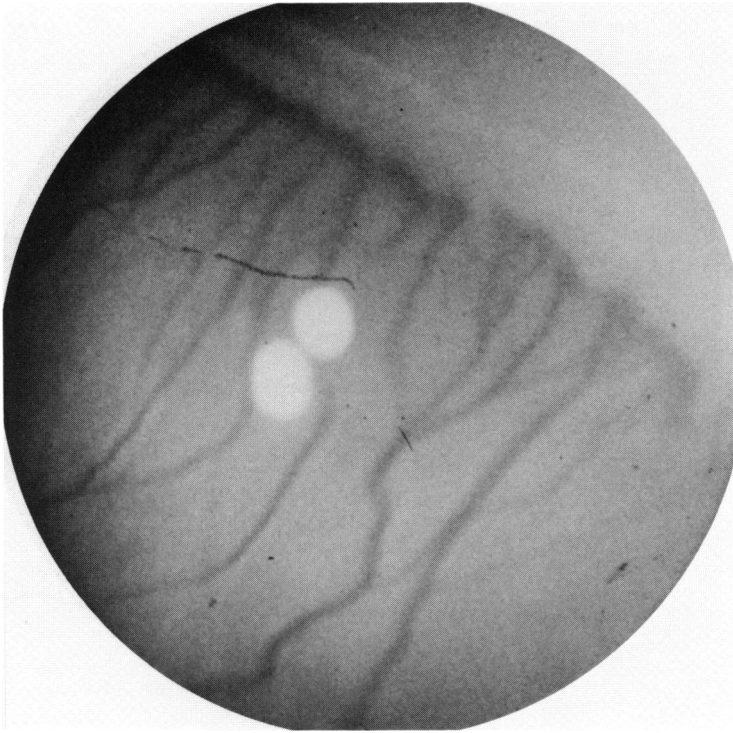


FIGURE 4

Fundus photograph of extraretinal fibrovascular proliferative tissue of stage 3.

CLINICAL APPLICATION

Having devised the above system, it then remained to systematically apply it to a study population. Commencing October 27, 1981, we have been conducting at the Bascom Palmer Eye Institute/Jackson Memorial Hospital Newborn Intensive Care Unit, a single-center, randomized, prospective trial of constant monitoring using the transcutaneous monitor in premature infants of birthweight less than or equal to 1300 gm. This study is designed to define quantitatively, if possible, the specific effect of oxygen on the incidence and severity of ROP. The design of this study is diagrammed in Fig 8. Thus far (March 15, 1984), 216 infants have been admitted to the overall study and it is from this patient pool that our classification study population was drawn (Table II). Since Nov 30, 1982, 121 patients have been discharged from the hospital with complete data

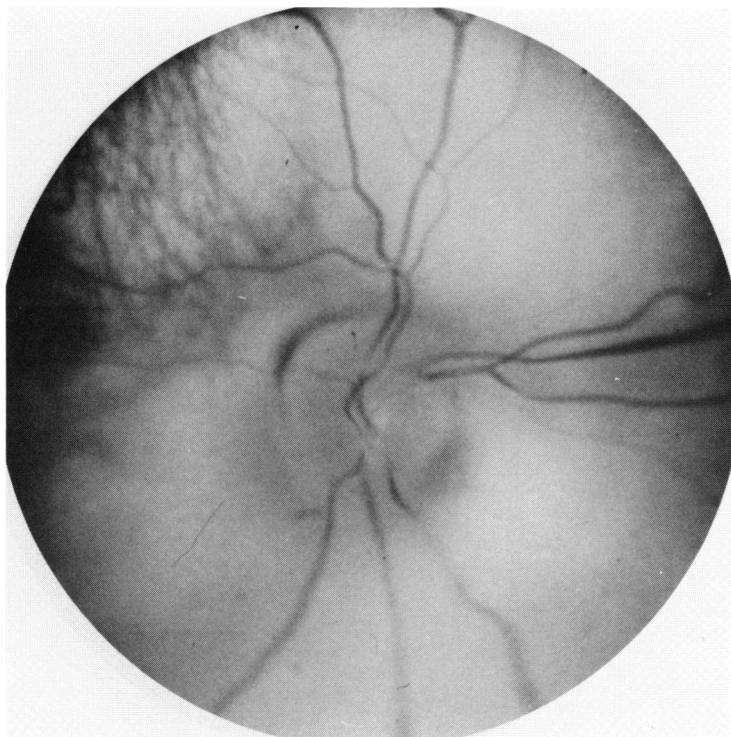


FIGURE 5
Fundus photograph of shallow exudative retinal detachment characteristic of stage 4 involvement.

recorded using the International Classification of ROP (ICROP). All examinations were performed by myself or my pediatric ophthalmology fellow on each infant every 2 weeks unless the medical condition of the infant precluded it. We were masked with respect to the identity of the infant examined, the results of the previous examinations, and the treatment status of the infant (whether continuously monitored or standard care). This has provided an internal control of the inter- and intraobserver reliability and accuracy.

PROFILE OF THE STUDY INFANT

The average infant in the study weighed just under 1 kg at birth and was approximately 29 weeks of conceptual age \pm (CA). The distribution of the infant's weight and CA at birth is plotted in Fig 9. Five weeks after birth

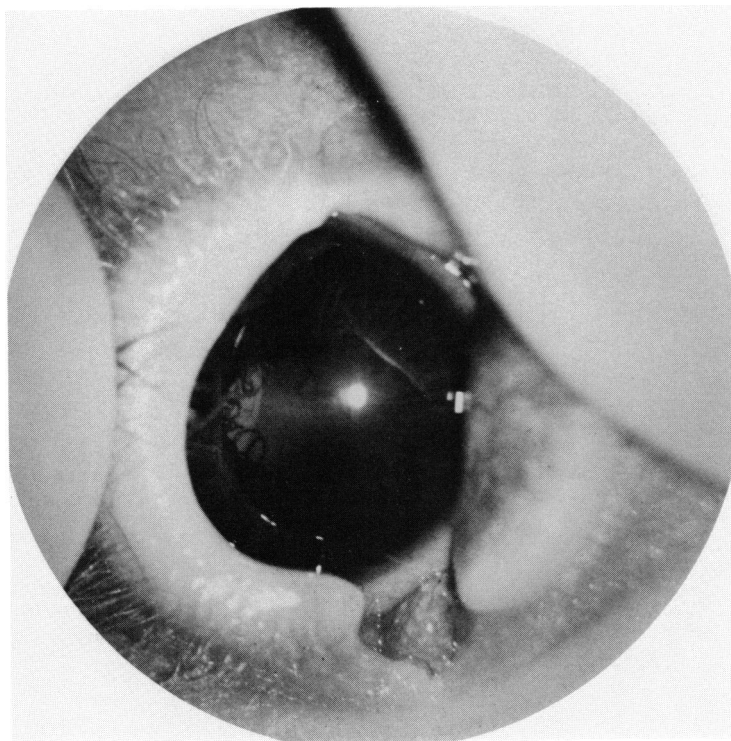


FIGURE 6
Iris vascular engorgement in plus disease.

the first examination was performed. There were 74 or 61% of the infants in this group who developed ROP. They were slightly smaller and were examined at a slightly later age on average than infants without the disease. For the most part, their diagnoses were made between the 32nd and 40th week of CA (Fig 10). The slight delay of the examination of these infants is probably the result of the “smaller-sicker” infant syndrome known to be associated with the occurrence of ROP today in contrast to the infants of earlier decades²² (Table III).

‡I use the term “conceptual age” throughout to relate all infants to the same time axis. Thus, an 8-week-old infant who was 26 weeks’ gestational age at birth is 34 weeks’ conceptual age when it reaches that 8-week mark. This is an entirely different infant physiologically and developmentally than an 8-week-old infant who was 36 weeks’ conceptual age at birth. By keeping the time axis constant, all infants are on the same developmental scale.

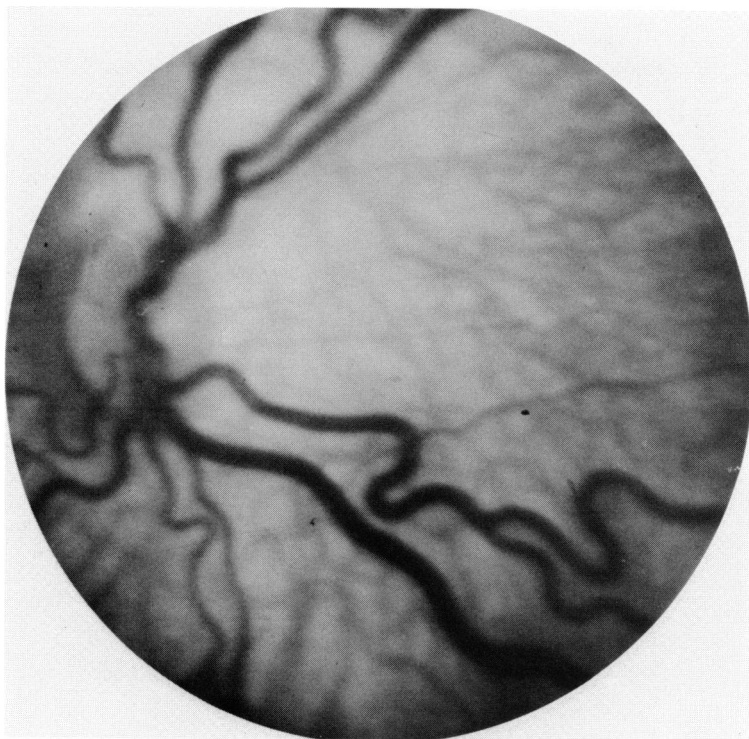


FIGURE 7

Fundus photograph of posterior venous dilatation and arteriolar tortuosity characteristic of "plus" disease.

PROFILE OF THE EXAMINATION RESULTS

To get at what the new classification told us about the type of ROP in the infants who developed it, I compared the disease as classified at two specific times: when it was first observed (± 37 weeks' CA) and when it reached its maximum during the infant's hospital stay (Table IV). Maximum examination was defined as that examination when at least two of the three parameters (location, extent, or stage) specified at each examination reached their highest in-hospital level. For practical purposes, this turned on the development of the most severe stage of the disease. Naturally, the disease continued on its course out of the hospital but we do not always achieve the regularity of follow-up as we do "in hospital" and, therefore, I chose that point to compare with the first observation of the disease.

TABLE I: RETINOPATHY OF PREMATURITY (ROP) OPHTHALMIC EXAMINATION RECORD

BIOGRAPHICAL DATA

Name _____ Hospital # _____

Birthdate (MM/DD/YY) ____/____/____ Sex (M = 1, F = 2) ____

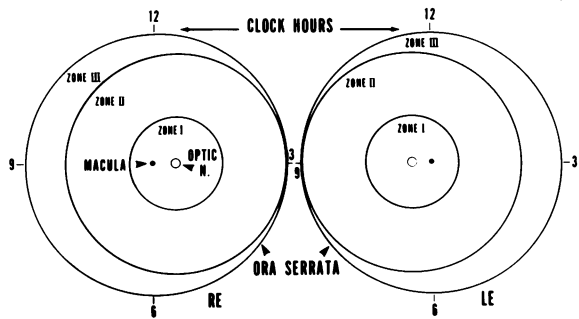
Birthweight (grams) _____ Gestational Age (weeks) ____

Multiple Births (Single = 1, Twin = 2, Triplet = 3) ____

EXAMINATION

Date of Exam ____/____/____

Examiner's Initials or # _____



ZONE

Mark with 'X'

Z 1

Z 2

Z 3

Z 1

Z 2

Z 3

STAGE AT CLOCK HOURS

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

Blank = normal

1 = Demarcation line

2 = Ridge

3 = 2+ Extraret prolifer

4 = 3+ Retinal detach

9 = No information

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

12□□12

11□□1

10□□2

9□□3

8□□4

7□□5

6□□6

Mark highest stage at every clock hour

☐ If Stage 3: 1 = mild, 2 = moderate, 3 = severe

☐

☐ If Stage 4: 1 = exudative, 2 = tractional, 3 = combined

☐

Other Findings

O.D.

Mark with 'X'

O.S.

☐ A Dilatation/tortuosity posterior vessels

☐

☐ B Iris vessel dilatation

☐

☐ C Pupil rigidity

☐

table 1 Cont .

☐ D Vitreous haze

☐ E Hemorrhages

☐

☐

Cicatricial RLF (Reese, 1953)

O.D.

Mark with 'X'

O.S.

☐ I. Small mass opaque tissue in periphery without detachment

☐

☐ II. Larger mass opaque tissue in periphery with localized detachment

☐

☐ III. Larger mass in periphery with traction fold to disc

☐

☐ IV. Retrolental tissue covering part of pupil

☐

☐ V. Retrolental tissue covering entire pupillary area

☐

COMMENTS:

Signature

As might be expected, location and extent remained constant and stage proved to be the variable that differed between the first and the follow-up examinations. It was gratifying to note that the zoning and the judgment of the disease's extent proved reliable between the two masked observers. For purposes of further analysis, the data was stratified into two birthweight strata, less than 900 gm and 900 to 1300 gm strata. Mortality and morbidity data, as well as our own prior incidence figures of ROP, suggested that this might be a natural division. What emerged again suggests a biological regularity to the disease which the new ICROP seems to capture quite well. In the lower birthweight strata, the disease tends to occupy zones I and II and the circumference of the developing vasculature. In the heavier birthweight strat, thereis more peripheral

TABLE II: PREMATURE INFANTS: BIRTHWEIGHT ≤ 1300 GRAMS (THROUGH 3/15/84)	
Total population monitoring study	216
a. Population classified by ICROP	137
(Infants still hospitalized 3/15/84)	– 16
b. Study population	121
Infants with ROP	74 (61%)

ROLE OF OXYGEN IN RLF

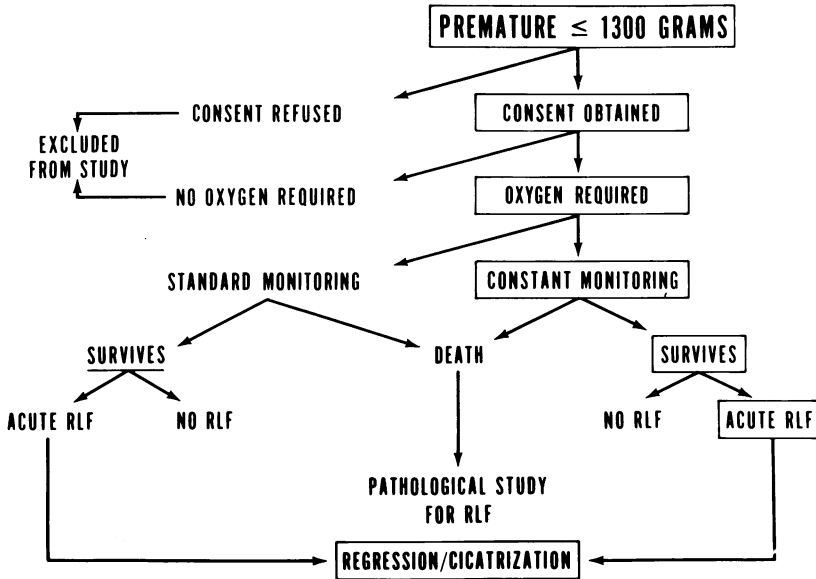


FIGURE 8

Flow diagram of randomized prospective trial of constant monitoring of oxygen therapy from which this study's patient population was drawn.

disease and the majority of it tends to occupy half to less than half the circumference of the developing vasculature. Three infants had shallow retinal detachments (stage 4) when first observed, while nine had reached this advanced stage by their maximum examination. The bulk of others seemed to plateau between stages 2 and 3 during their hospitalization. This latter variability in the overall distribution of staging of the disease between initial and the maximum stage may provide a valuable retrospective clue to the severity of the insult when looked at with larger numbers and in different centers.

LOCATION VS EXTENT VS STAGE—AN INTERNAL ANALYSIS OF THE PARAMETERS OF THE CLASSIFICATION SYSTEM

To carry the investigation one step further, I set each of the three parameters at the maximum hospital examination against one another. When examining the first parameter, the zone of the disease, against the second, its extent (Table V), the inner disease for the most part occupies over half

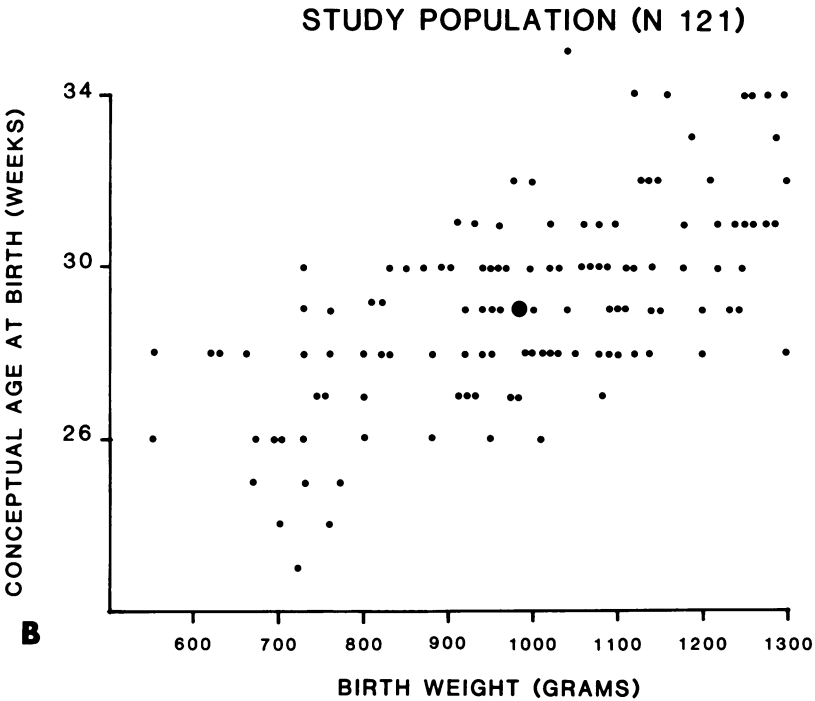
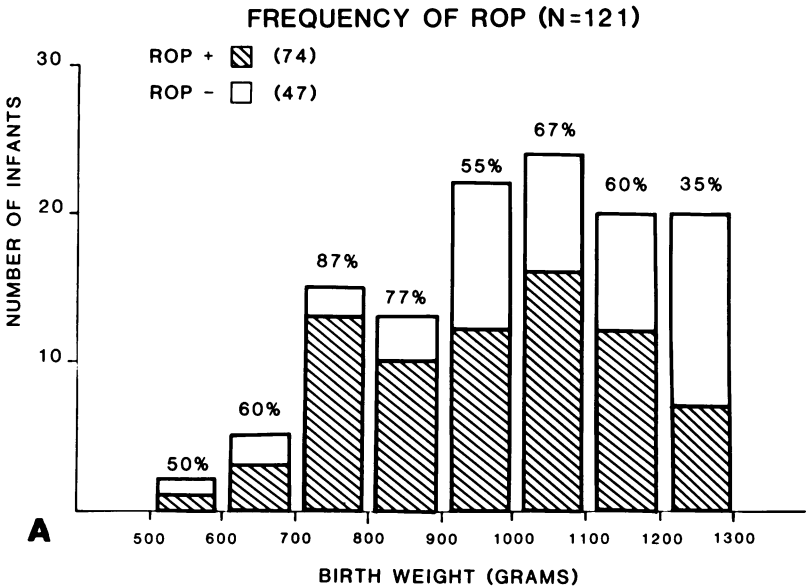


TABLE III: ICROP STUDY: PROFILE OF PREMATURE INFANTS, BIRTHWEIGHT \leq 1300 GRAMS

	MEAN \pm SD*
I. All infants (n = 121)	
A. Birthweight	989 \pm 188 gm
B. CA at birth	29 \pm 2 wk
C. CA at first examination	34 \pm 4 wk
II. ROP+ infants (n = 74)	
A. Birthweight	956 \pm 134 gm
B. CA at first + examination	37 \pm 3 wk
C. CA at maximum examination	39 \pm 4 wk

*Mean \pm standard deviation.

the circumference. Outer zone disease, presumably of later onset, tends to have half to slightly over half the circumference affected. When one, in turn, pits the extent against the stage, the same trend emerges (Table VI). The other side of this trend is seen most clearly when one looks at the final combination of the three variables, zone vs stage (Table VII). The majority of zone III disease never reaches a more severe stage than 2 or early stage 3.

There seems then to be apparent, at least in this preliminary study of a small sample of premature infants, a reasonably consistent trend among the three variables; location, extent, and stage. Since the first two, location and extent, are immediately visible on the earliest examination, this suggests that with further study of the variables a prognostic scale might be constructed for use early in the course of the disease useful in predicting its outcome.

"PLUS" DISEASE

This parameter, although not part of the classification system itself, is thought by some to be an independent measure of prognostic significance in ROP.²³⁻²⁵ Its major component, dilatation and tortuosity of the vessels of the posterior pole seems to follow from two factors, at least to this observer: the wipe-out of a large cross-sectional area of capillary bed by the initial insult to the developing endothelium with the creation of a large, high-pressure, high-velocity shunt²⁶ in the vascular bed of the eye. From the physics of non-Newtonian fluid flow in soft, distensible tubes,

FIGURE 9

A: Frequency histogram of incidence of ROP in each 100-gm birthweight strata. B: A scattergram of CA and birthweight in grams of all infants in this study.

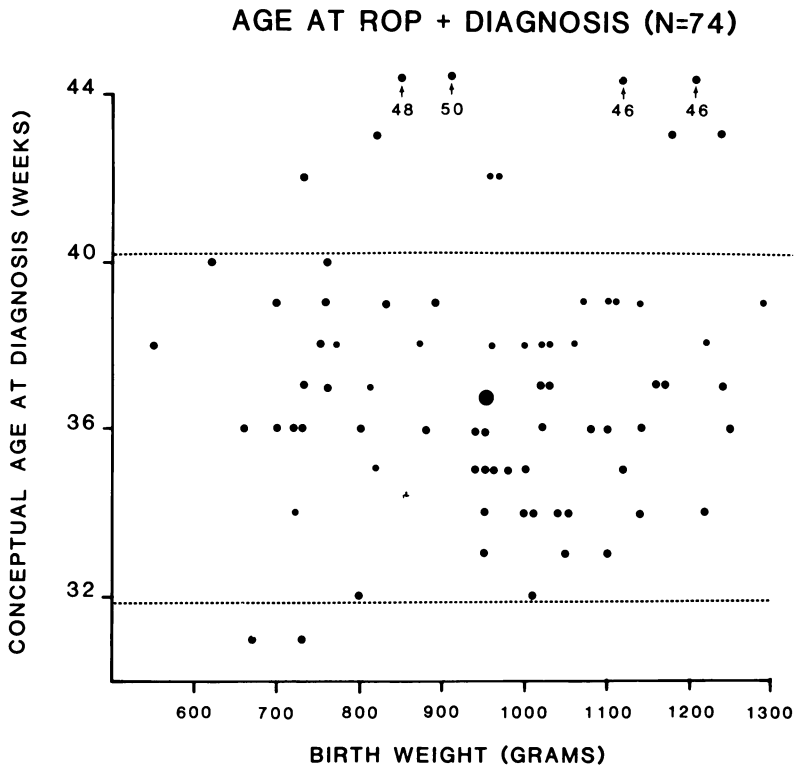


FIGURE 10

Birthweight in grams and CA at diagnosis for all infants with ROP at time of first diagnosis. The 8-week interval from 32 to 40 weeks encompasses all but 12 of diagnosed infants.

the development of all the characteristics of this sign of plus disease is inevitable and, in fact, predictable. In this series of infants, plus disease manifested by posterior dilatation and tortuosity, developed 13 times (Table VIII). Every time it developed, the disease was located in the inner zones, occupied 12 hours of vascular circumference and had reached either advanced stage 3 or stage 4. It remains to be demonstrated by further experience whether this sign carries any independent prognostic weight other than the primary variabes in the classification itself.

OUTCOME

What happened to the infants classified by this new system? For all infants, the answer is not yet available. But of the infants whose disease

TABLE IV: ROP(+) INFANTS (n = 74)

BIRTHWEIGHT STRATA (gm)	FIRST POSITIVE EXAM					MAXIMUM EXAM				
	LOCATION ZONES I-III		EXTENT (CLOCK HOURS)	STAGES 1-4		LOCATION ZONES I-III		EXTENT (CLOCK HOURS)	STAGES 1-4	
500	I	2	6-12 26	4	2	I	1	6-12 26	4	6
-	II	18	≤ 5 1	3	6	II	19	≤ 5 1	3	11
				2	15				2	9
899	III	7		1	4	III	7		1	1
900	I	0	6-12 12	4	1	I	0	6-12 12	4	3
-	II	17	≤ 5 35	3	9	II	17	≤ 5 35	3	16
1300				2	29				2	21
	III	30		1	8	III	30		1	7

has run its course, four have serious cicatricial sequela (Table IX). Listed, in addition to their final outcome, are the parameters they demonstrated on their maximum in-hospital examination. Interestingly, two other infants with stage 4 detachments have spontaneously resolved and regressed. Although the detachments were small and never extended posteriorly, it does point out the amazing variability of the outcome in ROP.

DISCUSSION

This paper has presented a single institution's experience with the new classification of ROP over a period of 17 months. During that time, it has proven possible for two observers to use the new system in a reliable and reproducible fashion. It has not notably prolonged the examining time of the infant and it has proven adaptable to computer coding.

The unifying principle underlying the system is simple: the more posterior the disease and the more vascular circumference involved, the

TABLE V: ROP(+) INFANTS: ZONE \times EXTENT (MAXIMUM EXAMINATION)

ZONE	≤ 5 HOURS	6-12 HOURS
I	0	1
II	0	37
III	13	23*

*One regressing when first seen.

TABLE VI: ROP(+) INFANTS: STAGE \times EXTENT
(MAXIMUM EXAMINATION)

STAGE	≤ 5 HOURS	6-12 HOURS
1	6	2*
2	7	23
3	0	27
4	0	9

*One regressing when first seen.

more serious the prognosis. It remains to be seen by usage throughout the world (it is hoped) whether, in fact, this assumption is correct.

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TABLE VII: ROP(+) INFANTS: ZONE \times STAGE
(MAXIMUM EXAMINATION)

ZONE	STAGE			
	1	2	3	4
I	0	0	0	2
II	1	13	16	6
III	7*	17	11	1

*One regressing when first seen.

TABLE VIII: ROP(+) INFANTS: PLUS DISEASE \times LOCATION/EXTENT/STAGE

	Location:	I = 2 II = 11 III = 0
Plus disease + (13) \longrightarrow	Extent:	12 hr = 13
	Stage:	4 9 3 4 2 0 1 0

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TABLE IX: OUTCOME: ROP INFANTS

INFANT NO	CICATRICAL GRADE: R/L (REESE ¹)	LOCATION (ZONE)	EXTENT (CLOCK HOURS)	STAGE 1-4	PLUS DISEASE
1630616	V/V	I	12	4	+
1671888	V/IV	I	12	4	+
1677079	III/III	II	12	4	-
1717304	II/?	II	12	4	+

DISCUSSION

DR WILLIAM TASMAN. An agreed upon international classification of retinopathy of prematurity (ROP) is long overdue and I am delighted that one is finally at hand. As Doctor Flynn so correctly points out the classification of Reese et al served ophthalmology well during the era when monocular direct ophthalmoscopy was virtually the exclusive method of ocular fundus examination. However, as a result of the increased use of indirect ophthalmoscopy and fluorescein angiography over the last 25 years, several new observations about ROP were made both here and abroad and the need for a revised classification became apparent. Several were developed, but none gained worldwide acceptance and many led to confusion when interpreting the indications for treatment and its results.

The cornerstones of the International Classification of ROP are the location and extent of the disease in the retina. Location is determined by three zones centered on the optic disc, extent by hours of the clock, and staging by the degree of abnormal vascular response in the retina. Added to these factors is the presence or absence of "plus disease" which appears in the retina as dilatation of the veins in the posterior pole and tortuosity of the arterioles. Generally this is associated with a marked shunt and a significant area of avascular retina. Occasional exceptions occur, however, when only zone I is vascularized and "plus disease" develops in the absence of any ridge at all.

To test the validity of the International Classification Doctor Flynn and his pediatric fellow examined 121 premature infants in a masked fashion and later compared their findings from the first examination and those recorded when the ROP had reached its maximum intensity during hospitalization. They found that zoning and extent of the disease were documented with reliable consistency between the two observers. In addition they noted that location and extent of the disease remained fairly constant while the stage of the disease varied significantly, an observation that correlates well with our own observations of premature infants.

To personally sample the International Classification, I recently had the opportunity to review 33 unknown slides of ROP supplied by Doctor Flynn and was able to demonstrate a high degree of conformity to the test answers.

In addition we have used the classification in the newborn nursery since the end of 1983, and have found it eminently satisfactory. It has led to a confidence in identifying a high risk stage III eye with "plus disease." This stage is characterized by extraretinal fibrovascular proliferation which arises on the posterior aspect of the ridge, leaks fluorescein profusely, and contrasts with tufts of new vessels on the surface of the retina often present in an eye with a stage II ridge. These latter tufts have tight endothelial cell junctions and do not leak fluorescein.

In summary, I believe that we now have a workable classification of ROP that for the first time makes it possible for meaningful communication. It constitutes the necessary foundation upon which future attempts to identify high risk eyes and the effectiveness of therapy can be based.

I congratulate Doctor Flynn and his 22 collaborators on their superb accom-

plishment, and hope that a similar effort can soon be undertaken to better classify the cicatricial stages of this disorder.

DR JOHN PAYNE. I would like to compliment Doctor Flynn and his 22 collaborators on this tremendous contribution and ask him whether he would touch on the plans for the multi-centered control study regarding cryotherapy in the acute stage of the disease so that this group may be aware of those plans.

DR ALFRED SOMMER. The experts involved in this exercise purposely went to great lengths to include all parameters of potential prognostic value. The preliminary results that Doctor Flynn has presented indicate a number of these are closely correlated with one another. Certainly others will be found to have little significance. I expect that from future observations the classification can be greatly simplified for routine clinical use; the more rapidly this can be accomplished the more "universal" will be its application.

DR MARSHALL PARKS. I congratulate Doctor Flynn and collaborators for giving us this new classification of retinopathy of prematurity which will serve a great need. I would like to pose two questions. The first one, partially asked previously by Doctor Payne, is; How does this classification benefit therapy of retinopathy of prematurity? I think I have some insight into the expected answer, but perhaps others in the audience along with me would like to hear more about this from the essayist. I suspect that already this classification has been found to provide a better basis than the old classification for prognosticating the value of therapy. The second question is; How does this new classification which deals with the clinical course of this disease relate to the old classification that describes the various end stages? Can we, who do not see the patients during their nursery stay, but later see the end stage cicatricial pathology reconstruct the probable classification of the disease when it was active? I wonder if an attempt also will be made to better classify the end stage of the disease comparable to this new classification of the active phase of the disease.

DR JOHN T. FLYNN. I would like there to be more discussants so that we can rival the cataract people! First of all, I would like to thank everybody who has discussed the paper for their kind words. I want to tell you what the future of the classification is. The first application of the International Classification will be as the backbone of the randomized, prospective, clinical trial. The trial will be a multi-center, mini-diabetic retinopathy trial, of the effect of cryotherapy upon the natural history of the retinopathy of prematurity. This is already into the planning stage and we are using the International Classification to define the threshold stage for treatment. It has defined for all of us what the threshold for our therapy is and all of the eyes in this study will be followed using this classification. That is, it's immediate and first application. The classification will be published here in the United States in the pediatric and ophthalmological literature and we are

hoping that it will be picked up and published elsewhere throughout the world. With regard to the end stages of the disease, retrolental fibroplasia, immediately following publication of this classification of acute disease, we are organizing a small group of retina-vitreous surgeons to work on this important next step as I see it. This next step is a classification of the so-called "cicatricial" phases of the disease under the viewpoint of their decreasing surgical prognosis. This is clearly the next logical step and we intend to take it.